REMARKS

Status of the application

Claims 1-21, 23, 25-26, and 29-47 are pending in the subject application, with claims 1-20 and 40-47 being withdrawn as directed to non-elected inventions, claims 31 and 35-39 being withdrawn as directed to non-elected species, and claims 21, 23, 25-26, 29-30 and 32-34 stand rejected in the instant office action.

Applicants provide the following remarks to address the issues raised by the instant Office Action.

Lack of response to Applicants' previous arguments

In the instant Office Action, the Examiner maintained the written description rejection and enablement rejection. However, the Examiner did not provide any comments or response regarding Applicants' previous arguments against these rejections which were submitted in Applicants' previous response. Accordingly, Applicants respectfully request that the Examiner consider the evidence and reasoning set forth in Applicants' earlier arguments. In addition, Applicants provide the following additional remarks to address these rejections and other issues raised in the instant Office Action.

Written description rejection under 35 USC §112, 1st paragraph

Claims 21, 23, 25-26, 29-30, 32-34 remain rejected under 35 USC §112, 1st paragraph for allegedly not in compliance with the written description requirement. In maintaining the rejection, the Examiner asserts that the claims broadly encompass the various genus of bacterial infection. However, the Examiner did not provide any specific reasoning as to why the claimed

invention is not described in the specification. Instead, the reasoning advanced by Examiner appears to be directed to whether a skilled artisan would be able to carry out the claimed invention.

With due respect, Applicants note that the Examiner has apparently confused the written description requirement with the issue of enablement. Therefore, Applicants will address the Examiner's other reasoning in maintaining the instant rejection below together with the enablement rejection. Nonetheless, Applicants provide the following remarks to further illustrate that the subject application meets the written description requirement.

It is well established that, in order to satisfy the written description requirement, a specification "need not teach, and preferably omits, what is well known in the art." See *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). As explained in the Applicants' previous response, the subject specification has adequately disclosed and described the claimed invention to the extent it is directed to the genus of bacterial infections. Bacterial infections *per se* are not Applicants' invention. Instead, bacterial infections are all well known in the art. Therefore, the written description requirement does not demand an exhaustive list of all bacterial infections that might be encompassed by the claimed invention. Nevertheless, the subject specification does provide an extensive disclosure and representative numbers of bacterial infections suitable for the claimed methods (see, e.g., pages 25-26).

In addition to the recited genus of bacterial infections, the subject specification has provided extensive description of

how to generate reactive oxygen species such as ozone in vivo to kill or inhibit the growth of bacteria, including how to providing antibody activity, sources of singlet oxygen, and methods of evaluating anti-microbial activity and effective dosages. For example, antibodies to be administered to a subject are described in the specification, e.g., at page 20, 2nd full paragraph; page 21, 2nd and 3rd paragraphs; page 22, 4th paragraph; page 26, 3rd full paragraph; and pages 29-37. Antibody-catalyzed generation of reactive oxygen species and sensitizer molecules used therein are described in the specification, e.g., at page 21, 1st and 4th paragraphs; and page 23, 2nd to 5th paragraphs. In addition, pharmaceutical compositions comprising an antibody, as well as administration routes and dosages thereof, are also described in the specification (e.g., pages 37-41). Moreover, the specification further provides more detailed guidance and specific procedures for practicing the present invention with exemplified bacterial species such as Escherichia and Salmonella (see, e.g., Examples III and IV).

Based on the extensive descriptions in the specification, it is an inescapable conclusion that the pending claims as well as all the elements recited therein are sufficiently described in the specification. Applicants accordingly respectfully request that the instant rejection be withdrawn.

New matter rejection under 35 USC §112, 1st paragraph

Claims 21, 23, 25-26, 29-30, 32-34 are newly rejected as allegedly containing new matter. The Examiner asserts that the phrase "via production of ozone" in a mammal constitute new matter. Applicants respectfully traverse this rejection for the reasons stated below.

Applicants first note that the Examiner apparently has applied a verbatim and literal support standard in making the instant rejection. However, such is not the legal test for written description requirement. Rather, the written description requirement "does not require in haec verba antecedence in the specification." Staehelin v. Secher, 24 USPQ2d 1111, 1117 (Fed. Cir. 1991; emphasis added). All that is required is that "the description convey with reasonable clarity to person of skill in the art that the inventor was in possession of whatever is now claimed." Vas-Cath v. Mazurka, 935 F.2d 1555, 19 USPQ2d 1111,1117 (Fed. Cir. 1991). If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Consistent with the case law, the MPEP also states that "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement." (MPEP § 2163.02; emphasis added). Further, it should be emphasized that mere rephrasing of a passage does not constitute new matter. "A rewording of a passage where the same meaning remains intact is permissible." See *In re Anderson*, 471 F.2d 1237 (CCPA 1973) and MPEP 2163.07-I.

Applying the above-noted legal standard to the instant case, it is readily clear that the phrase "treating bacterial infection in a mammal via production of ozone" has replete support in the subject disclosure. First, the specification disclosed methods of treating microbial infection in a mammal via reactive oxygen

species generated by an administered antibody. For example, at page 3, 2nd paragraph, the specification discloses:

> ". . . a method of treating a microbial infection in a mammal that involves administering to the mammal an anti-microbial composition consisting essentially of an antibody that can bind to a microbe, wherein the antibody can generate a reactive oxygen species when singlet oxygen ($^1O_2$) is present."

Second, throughout the specification, it is taught that antibodies have the ability to generate reactive oxygen species, that such reactive oxygen can kill microbes, and that such reactive oxygen species include ozone. For example, at page 13, last full paragraph, the specification discloses:

> ". . . antibodies, as a class of molecules, have the ability to convert singlet oxygen to reactive oxygen species. According to the invention, such reactive oxygen species can kill microbes. Examples of reactive oxygen species generated by antibodies include, but are not limited to ozone (O_3), superoxide radical (O_2^-), hydrogen peroxide (H_2O_2) or hydroxyl radical ($OH^\bullet$)."

Finally, the microbe infection to be treated with the claimed methods certainly include bacterial infection. See, the specification at, e.g., page 20, first paragraph.

Thus, the specification has disclosed (1) methods of treating microbial infections in a mammal via antibody-generated reactive oxygen species; (2) antibody-generated reactive oxygen species include ozone; and (3) microbial infections include bacterial infections. With such disclosures, there can be no doubt that the phrase "treating bacterial infection in a mammal via ozone production" is sufficiently supported by the subject

specification. It should be emphasized that, as explained above, written description does not require a literal and verbatim antecedence in the specification, and rephrasing of disclosures does not constitute new matter. If the Examiner chooses to maintain the rejection, Applicants respectfully request clarification.

Enablement rejection under 35 USC §112, 1st paragraph

Claims 21, 23, 25-26, 29-30 and 32-34 remain rejected as allegedly not enabled. In maintaining the instant rejection, the Examiner cited several prior art references as evidence that the "state of the prior art is unpredictable." The Examiner concluded from these references that "the art has not shown any anti-microbial composition consisting essentially of an antibody . . ., a sensitizer molecule . . ., wherein said compositions produces ozone in mammal for treating bacterial infection" (see the Office Action, at page 10, first paragraph). The Examiner further alleged that the examples disclosed in the specification only contemplate the claimed invention, and that the specification does not provide an example of an antimicrobial composition to treat bacterial infections. Applicants respectfully traverse the rejection for the reasons already on records and the additional remarks provided below.

A. **Lack of enabling disclosure in the prior art**

Examiner stated in the office action that the prior art did not show an antimicrobial composition comprising an antibody and a sensitizer molecule to produce ozone for treating bacterial infection. This is certainly true. Had it been otherwise, the claimed invention would not be novel in the first place. However, the Examiner appears to base the enablement rejection on

the fact that the prior art did not teach or enable the subject invention. In other words, the Examiner's logic seems to be that the claimed invention is not enabled because the prior art did not disclose the claimed invention. This is clearly an incorrect standard for enablement. Instead, the lack of teaching or enabling disclosure of the claimed invention in the prior art does not even remotely suggest that the subject disclosure does not enable the claimed invention. The issue of enablement for the subject invention primarily turns on whether disclosures of the subject specification teaches how to make and use the claimed methods. As detailed below, the answer to this question is undoubtedly in the positive.

B. **Enablement provided by the subject disclosure**

The correct test for enablement is whether the subject specification, in combination with knowledge from the prior art, teaches a skilled artisan to make and use the claimed invention without undue experimentation. The presently claimed invention is directed to methods of treating bacterial infection in a mammal via administering an antibody and a sensitizer molecule so that ozone is produced to exert the antimicrobial activity. To simplify the analysis, the issue of whether the claimed methods are enabled can be broken down to (1) enablement of administration of the recited antibody and the sensitizer molecule; (2) enablement of production of ozone by the administered antibody and the sensitizer molecule; and (3) enablement of bactericidal activity of ozone. As explained below, each of these elements of the claimed invention is enabled by the subject disclosure and/or knowledge well known in the art.

First, the claimed methods require the administration of an antibody and a sensitizer molecule to a mammal in need of

treatment for bacterial infection. As clarified above, antibodies and sensitizer molecules suitable for the invention are taught in great detail in the specification. The specification also disclosed that the administered antibody can be specific for the target microbe (see, e.g., page 22, third paragraph). Thus, for any given target bacterium, one can readily select an antibody that recognizes a surface antigen of the bacterium. For example, the antibody can be one that recognizes lipopolysaccharide (the common antigen present in the outer membrane of Gram-negative bacteria) or one that recognizes peptidoglycan (a common antigen present in Gram-positive bacteria and also in Gram-negative bacteria at lower levels). Such antibodies are all well known and routinely used in the art (see, e.g., USPN 6,315,999; and Bokisch et al., J. Exp. Med. 138: 1184-93, 1973). Similarly, various sensitizer molecules are also known in the art, with some specific exemplification set forth in the specification (e.g., page 23). It is readily apparent that these materials (i.e., the recited antibody and the sensitizer) can be readily obtained commercially or generated in accordance with the subject disclosure or knowledge well known in the art. In addition, as the Examiner certainly would not doubt, administration of the antibody and the sensitizer to a mammal is also enabled because no undue experimentation will be required.

Second, antibody-catalyzed production of reactive oxygen species (including ozone) in vivo from a source of singlet oxygen (e.g., a sensitizer molecule) is undoubtedly also enabled in the present application. This element of the claimed invention is the essence of the scientific findings from which the invention is derived. Thus, throughout the specification, it was taught that antibodies have the intrinsic ability to catalyze the conversion of singlet oxygen into reactive oxygen species. The

specification also taught and experimentally demonstrated that ozone is produced by isolated antibodies (e.g., page 82) or antibodies on activated neutrophils (e.g., at page 85). The specification additionally exemplified bacterial killing with antibody-generated reactive oxygen species against *E. coli and S. typhimurium* (see, e.g., Examples 3-4). These disclosures clearly demonstrated that bactericidal activity can be derived from antibody-catalyzed ozone production.

Further, while the specification only exemplified killing of Salmonella and Escherichia, the claimed methods are surely enabled to the extent that they can be equally applied to other bacterial infections. This is because the bactericidal activity of reactive oxygen species, e.g., ozone, is a broad-spectrum activity and is not limited to any specific bacterial species or microbe. Such a broad-spectrum antimicrobial activity is unequivocally taught in the art. For example, as noted in one of the references cited by the Examiner, Sunnen (pgs. 1-4, Ozonics International, 2005),"the inhibitory and lethal effects of ozone on noxious organisms have been observed since its discovery by Schonbein in 1840 . . . ." Consistently, there have been numerous reports in the art of ozone-mediated killing of various bacterial species, e.g., Escherichia coli, Bacillus cereus, Bacillus megaterium, coliform bacteria, Staphylococcus aureus, and Aeromonas hydrophilia. See, e.g., Broadwater et al., Appl. Microbiol. 26:391-3, 1973; Burleson et al., Appl. Microbiol. 29:340-4, 1975; Dyas et al., J. Clin. Pathol. 36:1102-4, 1983; and Lohr et al., J. Aquaric. Aquat. Sci. 4:1-8, 1984. Admittedly, these prior art studies did not employ a system of antibody-generated ozone production as presently claimed. However, the chemical nature and biological activity of ozone produced from the antibody-catalyzed reaction as presently

disclosed are surely the same as that of the ozone employed in the prior art studies. Hence, there can be no question that the present disclosure and the prior art enable bacterial killing via antibody-catalyzed ozone production with respect to other bacterial species not specifically exemplified in the subject specification.

Morever, the Examiner apparently faulted Applicants' invention for not providing an in vivo example of the claimed methods. It is acknowledged that the subject specification did not actually exemplify the claimed methods in a mammal subject. However, this by no means negates the enabling nature of the claimed invention. Rather, it is well established in the law that enablement of a claimed therapeutic method does not turn on actual exemplification. Instead, according to the MPEP, data obtained from in vitro studies can provide enablement for a claimed in vivo method if there is a correlation between the in vitro data and the claimed methods (see MPEP § 2164.02). In addition, it is the Examiner's burden to "give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model (MPEP § 2164.02). Thus, the issue in the instant case is whether the in vitro data demonstrating antibody-catalyzed ozone production and the accompanying bactericidal activity are reasonably correlated with an in vivo application as claimed. The Examiner has not advanced any convincing reasoning or evidence to show that such a correlation does not exist in the present case. To address this issue, the Examiner is advised to focus on the fact that the claimed invention is dependent on (1) the intrinsic catalytic activity underlying antibody-catalyzed ozone production, (2) the broad spectrum bactericidal activity of ozone due to its chemical nature. This intrinsic activity of antibodies and the chemical nature of ozone strongly suggest that

the in vitro exemplification can be reasonably extrapolated into an in vivo setting as presently recited. Such an extrapolation is also supported by the disclosed data that antibodies on activated neutrophils can produce ozone with bactericidal activity (see, page 85 in Example 3). Should the Examiner nonetheless question the enabling nature of this element of the claimed invention, Applicants urge the Examiner to provide scientific evidence or convincing reasoning as to why the demonstrated in vitro activity would not be expected to similarly work in vivo.

For all the remarks and clarifications provided above, Applicants submit that the presently claimed invention is enabled by the subject disclosure and the prior art. Withdrawal of the instant rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the claims now pending in the subject patent application are in condition for allowance, and notification to that effect is earnestly requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

The Director is hereby authorized to charge our Deposit Account No. 19-0962 in the event that there are any additional charges associated with the present Petition or any Response in connection with this application.

Respectfully submitted,

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Date

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